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## (54) DIARYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS

DIARYLHARNSTOFFDERIVATE UND DEREN VERWENDUNG ALS CHLORIDKANALBLOCKER

DERIVES DE DIARYLUREE ET LEUR UTILISATION COMME BLOQUEURS DE CANAUX CHLORURE

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**WO-A-02/064128**
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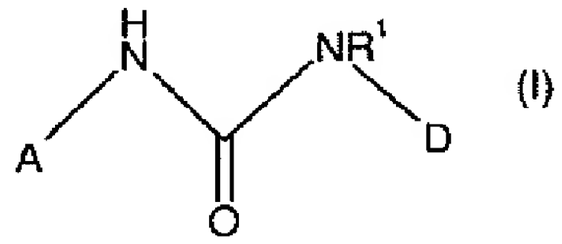
*N*-(2,6-Dichlooro-pyridin-4-yl)-*N*'-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 201-203°C;
*N*-(2,6-Dichloro-pyridin-4-yl)-*N*-[4'-(*N*',*N*'-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea; M.p. 163.8-164.5°C;
*N*-(2,6-Dichloro-pyridin-4-yl)-*N*-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 231-233°C;
*N*-[5-Chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-*N*-(pyridin-3-yl) urea; M.p. 214-220°C;
*N*-[4-Bromo-2-(1*H*-tetrazol-5-yl)-phenyl]-*N*-(pyridin-3-yl) urea; M.p. 193-194°C;
*N*-[2,4-Dibromo-6-(1*H*-tetrazol-5-yl)-phenyl]-*N*-(2,6-dichloro-pyridin-4-yl) urea; M.p. 202-203°C;

## Claims

**1.** A chemical compound represented by general formula (I)




(I)

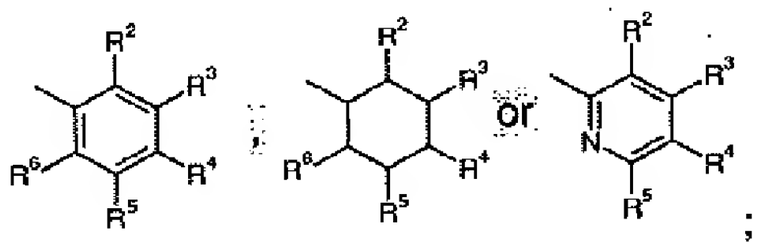
or a pharmaceutically acceptable salt thereof, wherein
A represents a ring system selected from the group consisting of:

pyridyl, thienyl, thiazolyl, indolyl, pyrazolyl and oxo-pyrrolidinyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

$R^1$ represents -H; and
D represents




;

wherein one of $R^2$, $R^3$, and $R^4$ is tetrazolyl;
and $R^5$, $R^6$ and the remaining one or two of $R^2$, $R^3$ and $R^4$ independently of each other represent:

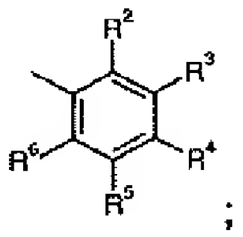
- hydrogen, halo, trifluoromethyl,
- -CH=CH-$COOR^b$, -$CH_2$-$CH_2$-$COOR^b$,
- -CO-$NR^b$-$CH_2$-$COOR^c$; -CO-$NR^bR^c$,
- -CH=CH-CO-$NR^bR^c$; -$CH_2$-$CH_2$-CO-$NR^bR^c$,
- piperidylcarbonyl,
- -NH-CO-$R^d$ or -NH-CO-NH-$R^d$;
  wherein $R^d$ is phenyl optionally substituted with one or more substituents independently selected from halo or trifluoromethyl; or
- phenyl optionally substituted with
  -$SO_2$-$NR^bR^c$, -CO-$NR^bR^c$, -CO-$NR^b$-$CH_2$-$COOR^c$, or piperidylcarbonyl; wherein $R^b$ and $R^c$ independently are hydrogen or alkyl.

**2.** The compound of claim 1, wherein

A represents pyridyl;
which pyridyl is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, and alkoxy; and

$R^1$ represents -H; and
D represents



;

wherein
$R^2$ represents tetrazolyl;
$R^3$, $R^4$, $R^5$, and $R^6$ independently of each other represent:

- hydrogen, halo, trifluoromethyl; or
- phenyl substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;
  wherein $R^b$ and $R^c$ independently are hydrogen or alkyl.

**3.** The compound of claim 1, being
*N*-(2,6-Dichloro-pyridin-4-yl)-*N*'-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
*N*-(2,6-Dichloro-pyridin-4-yl)-*N*'-[4'-(*N*",*N*"-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
*N*-(2,6-Dichloro-pyridin-4-yl)-*N*'-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
*N*-[5-Chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-*N*'-(pyridin-3-yl) urea;
*N*-[4-Bromo-2-(1*H*-tetrazol-5-yl)-phenyl]-*N*'-(pyridin-3-yl) urea;
*N*-[2,4-Dibromo-6-(1*H*-tetrazol-5-yl)-phenyl]-*N*'-(2,6-dichloro-pyridin-4-yl) urea;
or a pharmaceutically acceptable salt thereof.

**4.** A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-3, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

**5.** The use of a compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

**6.** The use according to claim 5, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a bone metabolic disease or an osteoclast related bone disease.

**7.** The use according to claim 5, wherein the disease, disorder or condition responsive to the blockade of chloride channels is osteoporosis, postmenopausal osteoporosis, secondary osteoporosis, osteolytic breast cancer bone metastasis, osteolytic cancer invation, Paget's disease of bone.

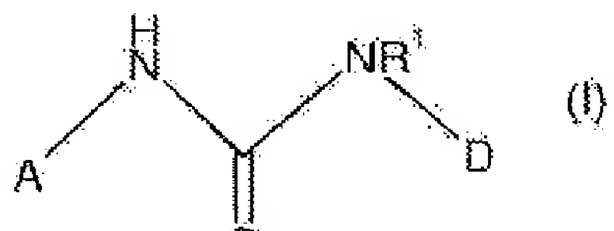
**8.** The use according to claim 5, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a disease, disorder or condition responsive to the mast cell or basophil activity, or to inhibition of angiogenesis.

**9.** The use according to claim 5, wherein the disease, disorder or condition responsive to the blockade of chloride channels is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction, anaphylaxis, asthma, atherosclerosis, atopic dermatitis (AD), bronchial

asthma, cancer, chronic obstructive pulmonary disease (COPD), Chrohn's disease, contact dermatitis, dilated cardiomyopathy, fatal asthma, graft rejection, hypersensitivity pneumonitis, ischemic hearth disease, pulmonary fibrosis, rheumatoid arthritis, systemic sclerosis, urticaria, uveoretinitis, cancer, metastatic cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma, lymphoma, exudative macular degeneration, age-related mucular degeneration (AMD), retinopathy, diabetic retinopathy, proliferative diabetic retinopathy, ischemic retinopathy (e.g. retinal vain or artery occlusion), retinopathy of prematurity, neovascular glaucoma, corneal neovascularization, rheumatoid arthritis, psoriasis, sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhea, hypertension, diuretic hypertension, glaucoma, or ulcers.

## Patentansprüche

1. Chemische Verbindung, die durch die allgemeine Formel (I) wiedergegeben wird



(I)

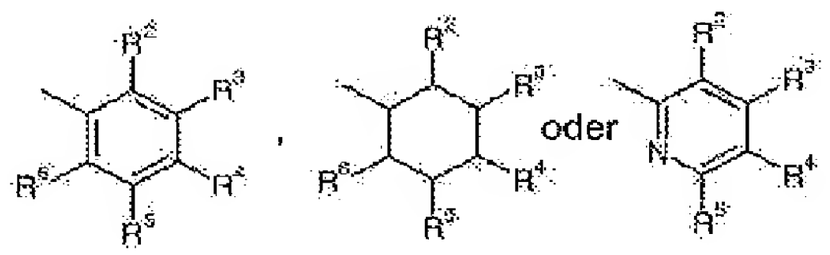
oder ein pharmazeutisch verträgliches Salz davon, wobei
A ein Ringsystem bedeutet, das ausgewählt ist aus der Gruppe bestehend aus:

Pyridyl, Thienyl, Thiazolyl, Indolyl, Pyrazolyl und Oxo-pyrrolidinyl;

wobei dieses Ringsystem gegebenenfalls mit einem oder mehreren Substituenten substituiert ist, die unabhängig voneinander ausgewählt sind aus der Gruppe bestehend aus:

Halogen, Trifluormethyl, Nitro, Alkyl, Alkoxy und Phenyl; und

$R^1$ -H bedeutet; und
D



bedeutet;
wobei eines von $R^2$, $R^3$ und $R^4$ Tetrazolyl ist;
und $R^5$, $R^6$ und die übrigen ein oder zwei von $R^2$, $R^3$ und $R^4$ unabhängig voneinander bedeuten:

- o Wasserstoff, Halogen, Trifluormethyl,
- o -CH=CH-$COOR^b$, -$CH_2$-$CH_2$-$COOR^b$,
- o -CO-$NR^b$-$CH_2$-$COOR^c$; -CO-$NR^bR^c$,
- o -CH=CH-CO-$NR^bR^c$; -$CH_2$-$CH_2$-CO-$NR^bR^c$,
- o Piperidylcarbonyl,
- o -NH-CO-$R^d$ oder -NH-CO-NH-$R^d$;

wobei $R^d$ Phenyl ist, das gegebenenfalls mit einem oder mehreren Substituenten substituiert ist, die unabhängig voneinander ausgewählt sind aus Halogen oder Trifluormethyl; oder